

# THE OBESE-ASTHMA PHENOTYPE



Rahul Nawander, ALMI, AALU  
Senior Consultant, Underwriting Research and Policy Development  
RGA International Corporation  
Toronto, ON  
rnawander@rgare.com

Obesity (body mass index > 30), already a known risk factor for hypertension, Type 2 diabetes, atherosclerosis and some forms of cancer, now presents with significant evidence as a major risk factor for asthma. Obesity-associated asthma presents a distinct clinical phenotype distinguished by later onset, higher prevalence in females, more symptoms than classic atopic asthma and with a relatively low degree of eosinophilic inflammation.



As reviewed by Weiss and Shore<sup>[1]</sup>, asthma incidence has increased in obese individuals. Obese or overweight individuals account for 75% of emergency department visits for asthma<sup>[2]</sup>. Numerous studies indicate that the relative risk of incident asthma increases with increasing obesity. Studies<sup>[3]</sup> have also observed that weight loss in the morbidly obese leads to a reduction in the severity and symptoms of asthma. Thus, it seems instead of asthma predisposing obesity, it is obesity that might cause and/or worsen asthma.

## Pathophysiology

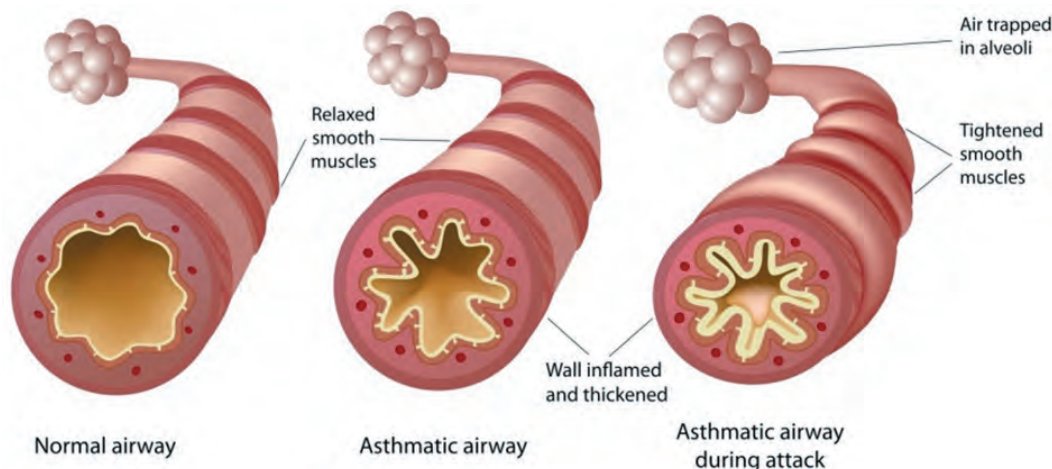
Obesity is frequently encountered in asthmatic applicants and it is therefore important to understand the pathophysiology of this phenotype to determine whether obesity is a comorbid factor affecting response to asthma therapy or is secondary to disease-driven inactivity in asthmatics.

The pathophysiology in this clinical phenotype appears to be multifactorial and is likely to involve a combination of possibilities including in utero conditions, genetic factors, comorbidities and inflammation secondary to excess adipose tissue. Some of these possibilities, which signify the influence of obesity on airway smooth muscle function ultimately leading to acute airway narrowing and airway hyper-responsiveness, are discussed below. [see Figure 1, next page]

**Executive Summary** *Obesity, a well-recognized risk factor for diabetes, coronary artery disease, as well as a few cancers, and is also an important risk factor for asthma and can present itself as a distinct asthma phenotype. Obesity also commonly encountered amongst insurance applicants with a diagnosis of asthma might present with higher morbidity risk when compared with normal-weight asthmatic individuals. A deeper understanding of the pathophysiological mechanism of this process explains how this distinct phenotype can lead to poor asthma control in obese individuals. As a result, obese-asthmatics are likely to present with additional morbidity costs in terms of increased health care utilization, significant loss of working days and an overall poorer quality of life. This article discusses this phenotype, and explains the pathophysiological mechanism and impact of this on morbidity, disability and health care utilization in obese-asthmatic individuals.*

- The first possibility regards the simple mechanics of increased intra-abdominal and chest wall mass and increased pressure on the diaphragm and chest wall.
  - o The increased intra-abdominal and chest wall mass causes lower than normal functional residual capacity. This change in functional residual capacity likely results in unloading (elastic load reduction) of airway smooth muscle, resulting in excess muscle fiber shortening and thus narrowing the airway.
  - o With increased intra-abdominal pressure on the diaphragm and chest wall, obese individuals breathe at higher rate but at a substantially smaller tidal volume. This tidal action of spontaneous breathing imposes tidal strains on airway smooth muscle, and these tidal strains are the most potent of all known bronchodilating

Figure 1. Airway smooth muscle in asthma (adapted from www.images.google.com)



mechanisms. Since this potent bronchodilating mechanism is compromised, it predisposes towards increased airway responsiveness.

- The second possibility addresses differences observed in the anatomy of the lungs and airways in obese individuals.
  - o In obese children, the mechanical load of obesity could affect lung growth, leading to smaller lung size and thus reducing the pulmonary function—a risk factor for asthma. This hypothesis can be postulated from a study<sup>[4]</sup> on leptin-deficient mice (leptin is a hormone that induces satiety and increases metabolism) that were morbidly obese in their early development and grew with substantially smaller lungs than lean wild-type mice.
  - o Obesity also likely leads to more accelerated airway remodeling with each asthma exacerbation. This has been observed from a study<sup>[3]</sup> that reviewed the effect of weight reduction on respiratory function in obese asthmatics. The study noted that weight loss did improve pulmonary function, but airway responsiveness remained unaltered. This finding endorses the role of obesity in airway remodeling, which is often not reversible.
- The third possibility explaining the role of obesity in asthma involves the inflammatory microenvironment.
  - o Adipose tissue, which is metabolically active and regulates energy homeostasis, has significant pathological effects that result in many obesity-related disorders. Adipose tissue itself has been identified to play an important role in chronic, low-grade systemic inflammation in obese individuals despite any overt inflammatory insult. This tissue infiltrated by

bone marrow-derived macrophages, secretes pro-inflammatory adipokines and cytokines, which result in a chronic inflammatory state. These obesity-related increases in cytokines including TNF- $\alpha$ , expressed on airway smooth muscle, have been shown to increase in vitro contractility of airways. Obesity is also associated with increased leptin and resistin (pro-inflammatory hormones) and decreased adiponectin (a protein hormone with potent anti-inflammatory effects). This chronic state of inflammation derived from adipose tissue in obese individuals alters the airway smooth muscle function, thus promoting airway narrowing. This pathophysiology also results in decreased glucocorticoid response and explains how obesity may undermine the efficacy of inhaled corticosteroids in treatment of asthmatics, resulting in poor control and increased severity.

[See Figure 2, next page]

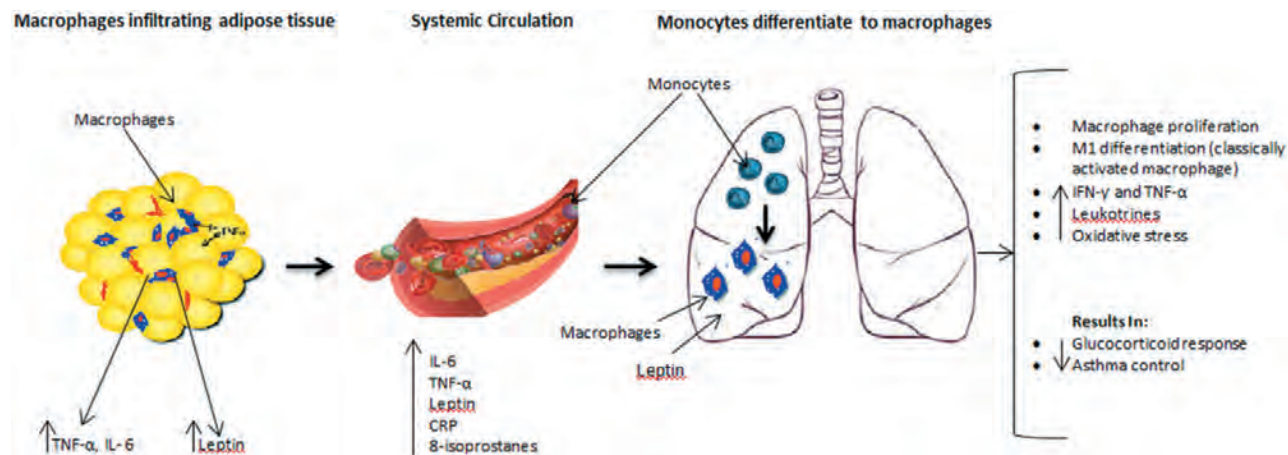
It is important for underwriters to note from the above-discussed mechanisms that obesity in absence of asthma can cause pathophysiological changes in lung function, including reduction in lung volumes, chest wall restriction and increased oxygen cost of breathing. These contribute to comorbid conditions such as gastroesophageal reflux and sleep apnea. These conditions might also cause dyspnea and wheezing, which at times could be mistaken for asthma.

#### Impact on morbidity, disability and health care utilization

Obesity can present itself as an etiology for asthma, while in known asthmatics it worsens the severity with poorer control, which leads to increased mor-



**Figure 2.** Adipose tissue in obese subjects produces pro-inflammatory cytokines that result in systemic inflammation with increased circulating levels of IL-6, TNF- $\alpha$  and leptin. Circulating monocytes are recruited into the lung where they differentiate into macrophages. Leptin plays a key role in macrophage proliferation and differentiation in the lung with subsequent secretion of pro-inflammatory cytokines. These alterations in pathophysiology result in poor asthma control<sup>[5]</sup>.



idity and greater health care utilization costs in comparison with normal-weight asthmatics.

A meta-analysis of prospective epidemiologic studies<sup>[6]</sup> which reviewed individuals from the US, Canada and Europe observed that the annual incidence rate of asthma in obese individuals (body mass index >30) was nearly twice that of normal-weight individuals (body mass index <25).

Obesity has been also found to be associated with increased severity in asthmatics determined by increased daily asthma symptoms, increased rescue bronchodilator usage and frequent night awakenings leading to significant loss of working days. This study<sup>[7]</sup> also observed that the association of obesity with severity remained unchanged when adjusted for factors such as age, gender and socioeconomics. Two studies<sup>[8][9]</sup> have also observed that obese asthmatics have a greater risk of hospitalization for acute asthma exacerbations and ultimately a poorer quality of life.

Obesity is also associated with decreased glucocorticoid responsiveness which in turn undermines optimum control with both inhaled corticosteroids (ICS) and combination therapies (inhaled corticosteroids plus long-acting bronchodilators). Multiple studies<sup>[10][11][12][13][14]</sup> have demonstrated that the response to inhaled corticosteroids is inversely correlated with increasing body mass index (BMI).

A limited number of studies<sup>[3]</sup> have investigated the impact of weight loss in obese asthmatics and noted a positive outcome. This clinical phenotype can be reversed by weight loss with improvements in lung

function, asthma control and asthma severity, with decreased medication utilization and hospitalizations. Dietary alterations could result in decreased markers of oxidative stress and inflammation in overweight individuals, which physiologically would help in reversing this phenotype. Although airway remodeling often cannot be reversed, weight management strategies could offer overall improvements in quality of life.

Asthma mortality declined by nearly 25% from 1999-2009 in the general US population<sup>[15]</sup>, which mostly is attributed to the introduction of novel inhaled corticosteroids and combination therapies. However, asthma prevalence rates have at the same time increased, from 7.3% in 2001 to 8.4% in 2010, when 25.7 million persons had asthma<sup>[16]</sup>. Health care utilization in asthmatics has increased with the number of visits to physician offices and emergency departments climbing by 7% to 8% since 1997. Most clinical and epidemiological studies indicate that this unique obese-asthma phenotype is more difficult to control and less responsive to asthma medications, which could lead to a further increase in health care utilization costs. This ushers in a new challenge in the underwriting of morbidity, especially for hospitalization and disability products.

### Summary

Both obesity and asthma are growing concerns for underwriting. With the evidence implicating obesity as a major risk factor for asthma, these two epidemics can now be linked. Numerous studies demonstrate a strong association between obesity and asthma, with the pathophysiological mechanisms of the former presenting a distinct phenotype which increases the

incidence of asthma, worsens severity, makes it difficult to control and less responsive to medications. This clinical obese-asthma phenotype if unchecked could possibly affect morbidity, significantly leading to increased health care utilization. Additional research findings could, in the near future, unveil the exact mechanisms that mediate this clinical phenotype and help in guiding novel therapeutic targets.

**Key** Obesity, a known risk factor for some of the most commonly encountered and significant underwriting impairments—Type 2 diabetes, atherosclerosis, hypertension, already presents with a significant mortality and morbidity risk. Furthermore, the association of obesity with asthma, which directly impacts incidence, severity and control, requires careful selection of risk by underwriters.

### References

1. Weiss ST, Shore, S. Obesity and asthma: directions for research. *American Journal of Respiratory and Critical Care Medicine* 169.8 (2004): 963-968.
2. Thomson CC, Clark S, and Camargo CA Jr. Body mass index and asthma severity among adults presenting to the emergency department. *CHEST Journal* 124.3 (2003): 795-802.
3. Aaron SD, et al. Effect of weight reduction on respiratory function and airway reactivity in obese women. *CHEST Journal* 125.6 (2004): 2046-52.
4. Shore SA, et al. Responses to ozone are increased in obese mice. *Journal of Applied Physiology* 95.3 (2003): 938-45.
5. Lugogo NL, Bappanad D, Kraft M. Obesity, metabolic dysregulation and oxidative stress in asthma. *Biochimica et Biophysica Acta (BBA)-General Subjects*. 2011; 1810(11): 1120-6.
6. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *American Journal of Respiratory and Critical Care Medicine*. 2007; 175(7): 661-6.
7. Taylor B, et al. Body mass index and asthma severity in the National Asthma Survey. *Thorax* 63.1 (2008): 14-20.
8. Mosen DM, et al. The relationship between obesity and asthma severity and control in adults. *Journal of Allergy and Clinical Immunology* 2008 Sep; 122(3):507-11.
9. Blandon VV, et al. Quality of life in pediatric patients with asthma with or without obesity: a pilot study. *Allergologia et Immunopathologia* 2004; 32(5):259-64.
10. Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respiratory Medicine* 2007 Nov; 101(11):2240-7.
11. Dixon AE, et al. Effect of obesity on clinical presentation and response to treatment in asthma. *Journal of Asthma*. 2006 Sep; 43(7):553-8.
12. Camargo CA Jr, et al. Effect of increased body mass index on asthma risk, impairment and response to asthma controller therapy in African Americans. *CMRO (Current Medical Research & Opinion)*. 2010 July; 26(7):1629-35.
13. Sutherland ER, et al. Body mass and glucocorticoid response in asthma. *American Journal of Respiratory and Critical Care Medicine*. 2008 Oct; 178(7):682-7.
14. Sutherland ER, et al. Body mass index and phenotype in subjects with mild-to-moderate persistent asthma. *Journal of Allergy and Clinical Immunology*. 2009 Jun; 123(6):1328-34.
15. Trends in asthma morbidity and mortality. American Lung Association, 2005. [www.fda.gov/OHRMS/Dockets/dockets/06n0454/06n-0454-bkg0001-16-Reference-13-ALA-vol4.pdf](http://www.fda.gov/OHRMS/Dockets/dockets/06n0454/06n-0454-bkg0001-16-Reference-13-ALA-vol4.pdf).
16. Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. *NCHS Data Brief*, no. 94. Hyattsville, MD: National Center for Health Statistics. 2012.

### About the Author

Rahul Nawander, ALMI, AALU, Senior Underwriting Consultant at RGA International Inc., specializes in underwriting research and development and assists on development of evidence-based underwriting guidelines for RGA. Rahul earned his degree in Health Sciences at Marathwada University in India and has worked in different facets of underwriting within RGA including automated risk assessment, training, product development and facultative underwriting. Rahul can be reached at [rnawander@rgare.com](mailto:rnawander@rgare.com) and is currently based in Toronto, ON.

The IBU team at the AHOU Expo in Washington.

